REMARKS

Prior to the present amendment, claims 15-18, 21-27 and 38-42 were pending. By this amendment, applicants have amended claim 42 and cancelled claim 24. Accordingly, claims 15-18, 21-23, 25-27 and 38-42 are currently pending.

In the Office Action dated June 22, 2004, claims 24 and 42 were rejected under 35 U.S.C. §112, second paragraph allegedly for lack of enablement. With regard to claim 24, applicants continue to assert that the composition of claim 24 is enabled as a preventative vaccine in accordance with the arguments and data presented in the Amendment dated December 12, 2003.

In order to facilitate prosecution, however, applicants have cancelled claim 24. Thus, the rejection of claim 24 under 35 U.S.C. §112 is now moot and should be withdrawn.

With respect to claim 42, the examiner states that the claim is directed to treating or preventing any viral infection or disease due to a viral infection by mucosally administering a vaccine formulation comprising HBsAg and a virus nucleocapsid or a virus-like particle. Thus, the examiner concludes that the claim requires undue experimentation.

Applicants have amended claim 42. Thus, claim 42 no longer is directed to a method for treating or preventing a viral infection. Instead, claim 42 as amended is directed to a method for administering a vaccine antigen which is a viral nucleocapsid or a virus-like particle. The method comprises administering mucosally a vaccine formulation of the claimed invention. Thus, the rejection of claim 42 under 35 U.S.C. §112 is now moot and should be withdrawn.

Claims 15, 16 and 21-23 were rejected under 35 U.S.C. §102(b) for allegedly being anticipated by Tabor et al. (U.S. Patent No. 4,547,368) in light of Bowen et al. (Research in Virology, 1992, 143:269-278, abstract only). The examiner states that Tabor et al. discloses a vaccine comprising HBsAg and HBcAg.

Tabor et al. does not, however, disclose mucosal administration. As the examiner acknowledges, Tabor et al. only teach subcutaneous injection of the antigen mixture.

In order to rectify the deficiency in Tabor et al., the examiner cites Bowen et al. According to the examiner, Bowen et al. teach that subcutaneous and nasally administered antigens generate **equivalent** immune responses. Therefore, the examiner concludes that the vaccine of Tabor et al. anticipates the claimed vaccine formulation suitable for mucosal administration.

The examiner further states that the citation of Tabor et al. in light of Bowen et al. is proper under U.S.C. §102. To support the examiner's assertion, she cites MPEP §2131.01 for the proposition that multiple references in a 102 rejection are proper when extra references are cited to show that a characteristic not disclosed in the reference is inherent.

Applicants respectfully disagree that the rejection is a proper §102 rejection. In a §102 rejection, the reference must disclose **each and every element of the claim**. Tabor et al. does not.

Applicants do not understand how the present claims can be said to be anticipated by Tabor et al. in view of Bowen et al. Clearly subcutaneous injection is **not the same** as mucosal administration, either explicitly or inherently. Therefore, the present claims cannot possibly be anticipated by Tabor et al.

In the rejection, the examiner states that Bowen et al. teach that subcutaneous and nasally administered antigens generate **equivalent** immune responses. However, in order for the rejection to be a proper §102 rejection, the claimed invention directed to a vaccine formulation suitable for mucosal administration would have to be **more than equivalent** to a vaccine formulation for subcutaneous administration. In fact, the vaccine formulation for mucosal

administration would have to be **identical** to the vaccine formulation for subcutaneous administration.

Thus, even if Bowen et al. taught that vaccine formulations for mucosal and subcutaneous administration generate equivalent responses, a §102 rejection is still not appropriate. Equivalency is not enough for an anticipation rejection. Each element of a rejected claim must be identical, either explicitly or inherently, to the same element in a reference. Tabor et al. does not, however, disclose a vaccine formulation for mucosal administration.

If the examiner contends that vaccine formulations for mucosal and subcutaneous administration generate an equivalent immune response, then rejection of the claims should be under 35 USC §103. In fact, Bowen et al. does not even teach that mucosal and subcutaneous vaccine formulations, in general, are equivalent.

Instead, Bowen et al. specifically teach that herpes simplex virus formulations, when administered subcutaneously or mucosally, result in **comparable** immune responses. Tabor et al. teach hepatitis virus vaccines. As is well known, hepatitis vaccines and herpes vaccines present very different issues and problems. Accordingly, Tabor et al. and Bowen et al. constitute non-analogous art.

In addition, contrary to the examiner assertion, Bowen et al. does not disclose that subunit formulations in general, delivered subcutaneously or mucosally, generate an equivalent immune response. It is incorrect for the examiner to extrapolate the teaching of Bowen et al. and conclude that antigens in general, when administered subcutaneously and nasally, generate an equivalent immune responses.

To support applicants' position that subunit antigens when administered subcutaneously and mucosally **do not** necessarily generate equivalent immune responses, attached herewith are

two references: 1) Thapar et al., *Vaccine* 1991, 9:129-133 (attached as Exhibit 1) and 2) Ghazi et al., *J. Med. Microbiol.*, 1995, 42:53-61 (attached as Exhibit 2).

Thapar et al. state in the last sentence of the abstract the following:

> These observations using a model ISCOM indicate that mucosal immune responses against membrane proteins were elicited in the female reproductive tract, and than ***non-mucosal immunization in the pelvis was a more effective route of administration than local application of the ISCOM to the vaginal mucosa.*** (*Emphasis added).*

Further, Thapar et al. state in the second paragraph of the "Introduction" section, the following:

> ... The only previous study of local, mucosal ISCOM immunization appears to be that of Lovgren, who found that two ***intranasal immunizations of mice with an influenza virus ISCOM produced lower serum titres of IgA and IgG antibodies than comparable subcutaneous administration*** *...(Emphasis added).*

The second reference, Ghzai et al., reports in the abstract the following:

> ... Immunisation of mice by the ***intramuscular route resulted in levels of serum IgG2a subclass antibody significantly greater than those induced by the same preparation given by the oral route...*** *(Emphasis added).*

Thus, the above citations of Thapar et al. and Ghzai et al. demonstrate that antigens, when administered subcutaneously and mucosally, **do not** necessarily generate equivalent

immune responses. Therefore, the examiner's generalization regarding the disclosure of Bowen et al. does not exist.

Accordingly, there is no disclosure or suggestion of vaccine formulations for mucosal administration comprising HBsAg and HBcAg in the cited references of Tabor et al. in light of Bowen et al. The claims are not even rendered obvious, let alone anticipated, by the references cited by the examiner.

For the above reasons, applicants respectfully request that the rejection of claims 15, 16 and 21-23 over Tabor et al. in light of Bowen et al. be reconsidered and withdrawn.

Claims 17, 25, 27 and 38-41 were rejected under 35 U.S.C. §103(a) for allegedly being obvious over Tabor et al. in light of Bowen et al. as applied to claims 15, 16 and 21-23, and further in view of Rose et al. (U.S. Patent No. 6,153,201) and Hauser et al. (U.S. Patent No. 5,972,346) for the reasons of record.

Applicants respectfully disagree. First, the rejection of claims 17, 25 and 27 will be addressed. Applicants have provided arguments above to refute the rejection of independent claim 15 over the primary references of Tabor et al. in light of Bowen et al.

The secondary references, namely Rose et al. and Hauser et al., were cited with respect to claims 17, 25 and 27, which depend on claim 15. The secondary references were not cited against independent claim 15. Therefore, the claims that depend on claim 15 (e.g., claims 17, 25 and 27) are patentable at least for the same reasons that claim 15 is patentable.

With regard to the rejection of claims 38-41, the examiner states that one of ordinary skill in the art would have been motivated to combine the HBsAg and HbcAg antigens of Tabor et al. in light of Bowen et al. with the HPV VLP of Rose et al to simultaneously treat or prevent

hepatitis B and papillomavirus infections. The examiner contends that Hauser et al. is cited for specifically teaching combination vaccines with HBV.

Applicants respectfully disagree that claims 38-41 are obvious over Tabor et al. in light of Bowen et al. and further in view of Rose et al. and Hauser et al. Applicants have provided arguments that Tabor et al. in light of Bowen et al. do not disclose or suggest vaccine formulations comprising HBsAg and HBcAg for mucosal administration. See above.

Rose et al. discloses the administration of HPV VLPs. There is no suggestion in Rose et al. to combine HBsAg with a second and third antigen, as is required in the claimed invention.

Hauser et al. discloses vaccine compositions that are administered intramuscularly (see column 4, lines 67). Nowhere in Hauser et al. is there any suggestion of a vaccine composition suitable for mucosal administration.

Further, there is no suggestion or motivation to combine Tabor et al. in light of Bowen et al., Hauser et al., and Rose et al. Hauser et al. states at column 3, lines 11-18 the following:

> Accordingly the hepatitis vaccine formulation according to an embodiment of the invention contains at least one other component selected from other hepatitis antigens, in particular hepatitis A antigen, or **non-hepatitis antigens which are known in the art to afford protection against one or more of the following: diphtheria, tetanus, pertussis, Haemophilus influenzae b, and polio**. *(Emphasis Added)*

Considering the emphasized words, Hauser et al. clearly provides a list of the non-hepatitis antigens to combine with HBV. The non-hepatitis antigens disclosed in Hauser et al. do not include HPV antigens, such as HPV VLP.

Accordingly, Hauser et al. does not suggest or provide motivation to combine HBV with HPV antigens, such as HPV VLP. Thus, there is no motivation to combine HBsAg as disclosed in Tabor et al. and Bowen et al., with HPV VLP as disclosed in Rose et al.

In addition, as stated in the Amendment dated December 12, 2003, Hauser et al., in fact, teaches away from combining HBV with HPV VLP. The examiner is invited to review the arguments presented in the Amendment dated December 12, 2003 at this time. In response, however, the examiner stated in the final Office Action that, although Hauser et al. do not list HPV, the broad range of other pathogen antigen examples acceptable for combination with the vaccine does not exclude other "non-hepatitis antigens" not specifically listed.

Applicants respectfully disagree with the examiner's position that Hauser et al. does not exclude other "non-hepatitis antigens" not specifically listed. Considering the above disclosure of Hauser et al. as a whole, a person having ordinary skill in the art would accept that the non-hepatitis antigens are the following: diphtheria, tetanus, pertussis, Haemophilus influenzae b, and polio. A person having ordinary skill in the art would **not** accept the non-hepatitis antigen to include HVP VLP.

Therefore, Hauser et al. does not teach combining HBsAg with HPV VLP.

Accordingly, applicants respectfully request that the rejection of claims 17, 25, 27 and 38-41 under 35 U.S.C. §103(a) be reconsidered and withdrawn.

Claims 15, 18 and 26 were rejected under 35 U.S.C. §103(a) for allegedly being obvious over Wands et al. The examiner states that Wands et al. discloses fusion protein comprising HBsAg and HCV core proteins. The examiner contends simultaneous administration of unfused HBsAg and HCV core antigens in a mixture would be equivalent to administering the fusion

protein of Wands et al. Therefore, the examiner concludes that the claimed invention is *prima facie* obvious, absent unexpected results to the contrary.

Applicants respectfully disagree that claims 15, 18 and 26 are obvious over Wands et al. As stated in the Amendment dated December 12, 2003, in order to constitute a reference against claims 15, 18 and 26, there must be motivation apparent in Wands et al. to convert fused antigens to unfused antigens. The examiner has not, however, provided the requisite motivation. Absent such motivation, a *prima facie* case of obviousness does not exist.

Further, the examiner provides no evidence to support her position that administration of unfused HBsAg and HCV core antigens in a mixture would be equivalent to administering the fusion protein of Wands et al. The administration of unfused antigens is **not** necessarily equivalent to administration of the antigens in a fusion protein for the reasons given below.

First, the antigens in a fusion protein are attached to each other. Therefore, the antigens in the fusion protein of Wands et al. are made in the same cell and necessarilly come in contact with the same cell. However, if the antigens are unfused, the unfused antigens may not contact the same cell.

Second, the antigenic epitope of each separate antigen may have a different conformation in a fusion protein due, for instance, to steric hinderance. However, if the antigens are unfused, each antigen retains its native conformation.

Therefore, administering the fusion protein of Wands et al. is not necessarily equivalent to simultaneous administration of unfused antigens, as the examiner asserts. As most, it may have been obvious to try simultaneous administration of unfused antigens. Suggestions to try, however, are not sufficient to sustain a *prima facie* case of obviousness.

Accordingly, the claimed invention containing a mixture of HBsAg and viral nucleocapsid or virus-like particle cannot be said to be obvious over Wands et al. Thus, applicants respectfully request that the rejection of claims 15, 18 and 26 under 35 U.S.C. §103(a) be reconsidered and withdrawn.

In view of the above remarks, allowance of the pending claims is earnestly requested. If the examiner has any questions regarding this amendment, the examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

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